SCIENTIFIC PAPER JSLS

Effectiveness of Gastric Neurostimulation in Patients With Gastroparesis

Jeremy Ross, MS, Mario Masrur, MD, Raquel Gonzalez-Heredia, MD, E. Fernando Elli, MD

ABSTRACT

Background: Patients with gastroparesis have significantly delayed gastric emptying because of impaired nerve function. Gastric neurostimulation from Enterra Therapy provides electrical pulses to the stomach tissue that promotes stimulation of stomach smooth muscle, thereby enhancing gastric emptying. This study evaluates the effectiveness of Enterra Therapy (Medtronic, Minneapolis, Minnesota) in reducing symptoms and improving the quality of life of patients with drug-refractory gastroparesis.

Material and Methods: In this study 25 patients underwent minimally invasive, laparoscopic placement of the Enterra Therapy device. Patients were asked to rank their severity of symptoms and quality of life retrospectively by completing the Gastrointestinal Symptoms Rating Scale and Short Form 36 Health Survey with respect to their condition before and 6 months after initiation of Enterra Therapy.

Results: Eighteen patients completed the surveys. Patients showed statistically significant improvement in their overall Gastrointestinal Symptoms Rating Scale scores and the mental health component of the Short Form 36 Health Survey.

Discussion: Currently, Enterra Therapy has Humanitarian Use Device status, which means that more clinical evidence is needed to prove its effectiveness in gastroparesis. By showing that Enterra Therapy reduces symptoms of gastroparesis and improves patient quality of life, this study contributes to the increasing amount of data supporting its use and potential Food and Drug Administration approval.

Key Words: Enterra, Gastric pacemaker, gastroparesis.

Division of General, Minimally Invasive and Robotic Surgery, Department of Surgery, University of Illinois at Chicago, Chicago, IL, USA (all authors).

Address correspondence to: Mario Masrur, MD, Division of General, Minimally Invasive and Robotic Surgery, University of Illinois at Chicago, 840 S Wood St, M/C 958, Ste 435 E, Chicago, 60612 IL, USA. Telephone number: (312) 355-4220; Fax: (312) 355-1987; E-mail: mmasrur@uic.edu

DOI: 10.4293/JSLS.2014.00400

INTRODUCTION

Patients with gastroparesis have delayed or inhibited gastric emptying of contents from the stomach into the small intestine.[1] Although the exact cause is unknown, gastroparesis usually stems from diabetic, idiopathic, or postsurgical etiology. In patients with gastroparesis, impaired nerve function fails to stimulate consistent smooth muscle contractions in the stomach. Common symptoms include weight loss from malnutrition, dehydration, nausea, vomiting, and loss of appetite.

Diagnosis of Gastroparesis

The gold standard for diagnosis of gastroparesis is a delayed gastric-emptying study. During a solid gastric-emptying study, patients ingest a solid meal containing radiolabeled sulfur colloid. The normal amount of time it takes for the stomach to empty half of its contents into the small intestine is typically 60 to 100 minutes.[1] Patients with gastroparesis may have emptying times with a half-life from just over 100 minutes to >500 minutes.[1] The first line of treatment for patients with symptoms of gastroparesis is usually diet modifications and use of pharmaceuticals such as ondansetron, metoclopramide, or domperidone for nausea, vomiting, and heartburn.

Enterra Therapy

When pharmaceuticals and dietary treatments fail, gastric neurostimulation may be offered to alleviate symptoms of gastroparesis. The goal of gastric neurostimulation is to stimulate smooth muscle contractions of the stomach. Currently, Enterra Therapy (ET) (Medtronic, Minneapolis, Minnesota) is the only Humanitarian Use Device (HUD) capable of providing gastric neurostimulation to patients with gastroparesis. The approval of ET as an HUD means that it has been proved not to harm patients but has not been proved effective in treating the symptoms of gastroparesis. As an HUD, the Enterra system can only be used in institutions consisting of an institutional review board that has approved the device and agreed to monitor its use in clinical trials.[2]

The ET system is composed of a small electrical generator that is surgically implanted beneath the skin of the abdo-

men and 2 electrodes that are surgically placed in the superficial tissue of the distal stomach. The ET system produces high-frequency electrical pulses to the stomach tissue, allowing for electrical stimulation of the stomach smooth muscle.[3] The physician can adjust the voltage and rate settings of the neurostimulator at any time based on the patient's symptoms. Past studies have shown ET to relieve symptoms of gastroparesis such as vomiting and nausea to varying degrees.[4,5] However, given limited data and the system's status as an HUD, more clinical evidence is needed to prove its effectiveness in reducing symptoms of gastroparesis. If it can be proved that ET safely and effectively reduces symptoms of gastroparesis, it may be considered more readily as a treatment option.

Gastrointestinal Symptoms Rating Scale

The Gastrointestinal Symptoms Rating Scale (GSRS) is a commonly used questionnaire to gauge patients' gastrointestinal symptoms. The GSRS is composed of 15 items that measure patients' symptoms in 3 domains: dyspepsia syndrome (5 items), indigestion syndrome (4 items), and bowel dysfunction syndrome (6 items).[6] For each item, patients choose a response, numbered 0 through 3, based on the severity and frequency of their symptom. A response score of 0 represents no symptom, and a response score of 3 represents a severe symptom with serious impact on daily life. Therefore, with respect to dyspepsia syndrome (which contains 5 items), a score of 15 represents the worst clinical symptoms and a score of 0 represents the best. The dyspeptic syndrome domain monitors symptoms such as abdominal pain, heartburn, acid regurgitation, sucking sensations in the epigastrium, and nausea and vomiting. The indigestion syndrome domain monitors borborygmus, abdominal distention, eructation, and increase in flatus. Lastly, the bowel dysfunction syndrome domain monitors decreased passage of stools, increased passage of stools, loose stools, hard stools, urgent need for defecation, and feeling of incomplete evacuation.

Short Form 36 Health Survey

The Short Form 36 Health Survey (SF-36) is a 36-question instrument used to measure patients' health-related quality of life. The SF-36 evaluates patients in 8 domains: physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health. These 8 domains contribute to 2 summary scores, the mental component summary and the physical component summary. For each domain and summary component, 0 represents the worst possible score and 100 represents the best possible score. This study uses norm-based scores to interpret the SF-36 results. This means that the SF-36 scoring algorithm that was used takes into account general population norms, such that the average population score for each domain is set at 50.[7] This allows for a more simplified interpretation of scores and allows scores to be compared with those from other studies using the SF-36.[8]

METHODS

Operative Procedure

Implantation of the Enterra device was performed laparoscopically in 25 patients at the University of Illinois Hospital in Chicago. A 5-mm trocar was placed in the right upper quadrant, another 5-mm trocar was placed through the umbilicus, and a 12-mm trocar was placed in the left flank. Two parallel leads spaced 1 cm apart were placed into the muscular layer of the stomach exactly 10 cm from the pylorus. Upper endoscopy was then performed to confirm that there had been no perforation of the gastric mucosa. The 2 leads were connected to the Enterra generator, which was then placed in the fascia of the left flank. The leads were directed through the 12-mm trocar in the left flank. Patients were discharged when in stable condition and were placed on a special gastroparesis diet. They were instructed to follow up in 3-month intervals, or as needed. During follow-up visits, adjustments were made to pacemaker settings if patients' symptoms persisted. The standard Lamborghini protocol was used for making pacemaker adjustments.

Survey Instruments and Statistical Analysis

The GSRS and the SF-36 were used to measure patients' severity of symptoms and health-related quality of life, respectively. Patients were asked to complete the GSRS and SF-36 surveys retrospectively with respect to their condition before and 6 months after implantation of the Enterra device. Patient responses for pre- and post-Enterra implantation were scored and found to follow a non-normal distribution according to the Anderson-Darling test for normality. As such, the data were analyzed using the Mann-Whitney *U* test. $P < .05$ was considered significant.

RESULTS

Patient Demographic Data

Twenty-five patients underwent laparoscopic placement of the ET device, with no surgical complications recorded. The mean hospital length of stay for patients was 2.8 days.

Of the patients, 92% were women (n = 23) and 8% were men (n = 2), with the mean patient age being 39.2 years (range, 20–65 years). Regarding race, 44% of patients (n = 11) identified as white, 44% as Hispanic or "other," and 12% as black (n = 3). Of these patients, 60% (n = 15) had gastroparesis of diabetic etiology whereas 40% (n = 10) had gastroparesis of idiopathic etiology. Patients had been diagnosed with gastroparesis, on average, 2.5 years before receiving ET. Of note, 48% of patients (n = 12) had a history of cholecystectomy, and 44% of patients (n = 11) had a history of anxiety, depression, or a personality disorder. Compared with cases of diabetic etiology, patients with idiopathic gastroparesis had higher rates of both cholecystectomy (60%) and history of anxiety, depression, or a personality disorder (60%). These statistics are summarized in **Table 1**.

Of the 25 patients receiving ET, 18 responded to the GSRS and SF-36 surveys; 89% of responders were women (n = 16) and 11% were men (n = 2). Nearly 95% of patients reported nausea and vomiting to be their most debilitating symptoms before receiving ET.

Table 1.
Summary of Patient Demographic Data, Gastroparesis Etiology, and Medical History

	Data
Average length of stay in hospital	2.8 d
Female patients (%)	92
Male patients (%)	8
Mean patient age (y)	39.2
Patient age range (y)	20–65
Patients identifying as white (%)	44
Patients identifying as black (%)	12
Patients identifying as Hispanic or other (%)	44
Diabetic gastroparesis (%)	60
Idiopathic gastroparesis (%)	40
Mean interval after diagnosis with gastroparesis (y)	2.5
Patients with history of cholecystectomy (%)	48
Diabetic cases with history of cholecystectomy (%)	40
Idiopathic cases with history of cholecystectomy (%)	60
Patients with history of anxiety, depression, or personality disorder (%)	44
Diabetic cases with history of anxiety, depression, or personality disorder (%)	33.3
Idiopathic cases with history of anxiety, depression, or personality disorder (%)	60

GSRS Results

On the basis of the GSRS, ET improved symptoms to varying degrees in 89% of patients (n = 16). Patients with improved symptom scores showed statistically significant improvement in the dyspeptic syndrome domain ($P < .01$) and indigestion syndrome domain ($P = .03$) of the GSRS but not in the bowel dysfunction syndrome domain ($P = .08$). Improvement in overall GSRS scores was found to be statistically significant ($P < .01$). **Table 2** shows the statistically significant reduction in overall GSRS, dyspeptic syndrome, and indigestion syndrome scores.

Figure 1 shows the median preoperative and postoperative GSRS domain scores for patients receiving ET.

SF-36 Results

According to the SF-36, ET significantly improved patient mental health component (MHC) scores, with a median improvement of 11.1 percentage points ($P = .01$). The physical health component (PHC) scores had a median improvement of 4.9 percentage points, but this improvement was not considered statistically significant ($P = .06$). **Table 3** shows the statistically significant improvement in the mental health summary component of the SF-36. Improvements in the physical health summary component yielded $P > .05$ and were therefore not considered statistically significant.

Figure 2 shows the median preoperative and postoperative summary scores of the SF-36. The SF-36 summary scores include the MHC and the PHC.

Patient Responses Based on Gastroparesis Etiology

Of the patients who completed the GSRS, 56% (n = 10) had gastroparesis of diabetic etiology and 44% (n = 8) had

Table 2.
Median Preoperative and Postoperative Scores for Each Domain of GSRS

	Preoperative Median	Postoperative Median	*P* Value
Overall GSRS score	25	12	< .01
Dyspeptic syndrome domain score	11.5	4	< .01
Indigestion syndrome domain score	7	3	.03
Bowel dysfunction syndrome domain score	6.5	5.5	.08

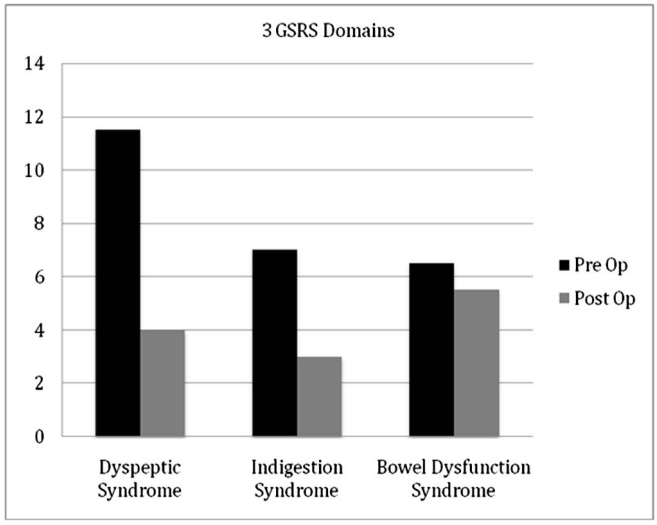

Figure 1. Median preoperative and postoperative scores for each GSRS domain.

Table 3.
Median Preoperative and Postoperative Scores for SF-36 MHC and PHC Summaries

	Preoperative Median	Postoperative Median	*P* Value
MHC score	29.15	46.6	.01
PHC score	28.5	31.1	.06

gastroparesis of idiopathic etiology. Both groups were found to have a statistically significant improvement in GSRS scores after receiving ET ($P = .03$ for diabetic cases and $P = .01$ for idiopathic cases). With the exception of 2 patients with idiopathic gastroparesis, all patients showed at least some improvement in their postoperative GSRS score.

Patient Response Based on History of Cholecystectomy

Of the patients who completed the GSRS, 56% (n = 10) had a surgical history of cholecystectomy whereas 44% (n = 8) did not. On the basis of the preoperative and postoperative GSRS scores, patients with a history of cholecystectomy responded better to ET than those without a history of cholecystectomy. After implantation of the ET device, patients with a history of cholecystectomy showed a statistically significant improvement in the GSRS ($P < .01$) whereas those without a history of cholecystectomy showed no statistically significant improvement ($P = .06$). Patients with a history of cholecystectomy differed most

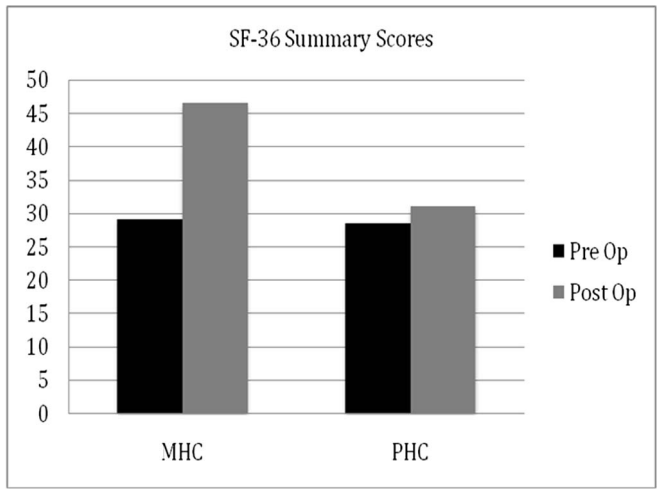

Figure 2. Median preoperative and postoperative SF-36 summary scores.

from patients without a history of cholecystectomy in the indigestion syndrome and bowel dysfunction syndrome domains of the GSRS. **Table 4** shows the *P* values for improvements in the GSRS domains for patients with and without a history of cholecystectomy.

DISCUSSION

Past studies have suggested that gastric electrical stimulation (GES) can be an effective way to treat patients with severe gastroparesis. In 2008 Velanovich[4] showed that roughly three-quarters of gastroparesis patients treated with GES showed improvement in their gastrointestinal symptoms, although the degree of improvement varied by individual. This study, along with others,[9,10] supports the idea that GES can be used to reduce symptoms such as nausea and vomiting in patients with diabetic and idiopathic gastroparesis.

In 2009 O'Grady et al[11] published the first meta-analysis evaluating high-frequency GES outcomes from 1992 to 2008. Studies included in the meta-analysis were selected based on similarities in the methods used to score patients' symptoms. This unfortunately led to exclusion of many studies from the meta-analysis. Because of limited numbers of controlled trials, only 1 of the 13 studies included in the meta-analysis was a randomized controlled trial, the rest being noncontrolled observational studies. Although the results of the meta-analysis must be interpreted with caution because of the quality of studies included, they do show significant benefits from ET. According to the meta-analysis, ET had the greatest benefits in patients because of its reduction of nausea and vomit-

Table 4.
P Values Associated With GSRS Improvements for Patients With and Without History of Cholecystectomy

	History of Cholecystectomy	No History of Cholecystectomy
Overall GSRS improvement	$P < .01$	$P = .06$
Dyspeptic syndrome improvement	$P < .01$	$P < .01$
Indigestion syndrome improvement	$P = .05$	$P = .1$
Bowel dysfunction syndrome improvement	$P = .05$	$P = .2$

ing episodes, as well as reduction in the need for enteral and parenteral nutritional support. In addition, of the 4 studies in the meta-analysis that used the SF-36 to track patients' health-related quality of life, overall significant improvements were noted in the MHC and PHC summaries. These demonstrated improvements in nausea, vomiting, and the MHC of the SF-36 are consistent with the significant improvement in the MHC and reduction in nausea and vomiting found in our study (nausea and vomiting measured by the dyspeptic syndrome domain of the GSRS).

In this study 89% of patients who completed the GSRS reported improvement, to some degree, in overall gastrointestinal symptoms. In addition, 83% of the patients reported increased MHC scores on the SF-36. These improvements were statistically significant with $P = .01$. Interestingly, patients who showed no improvement on the GSRS, as well as those without improvement in the physical component summary of the SF-36, all had improvement in the MHC of the SF-36. This means that even if patients did not believe that their symptoms had improved, they still felt better mentally after 6 months of ET. This finding of general improvement in the SF-36 MHC suggests that either ET had made patients better off mentally or patients had adjusted more over time to their condition and became better at managing the emotional challenges of their gastroparesis. For this reason, it is important not to overlook the impact of mental health in everyday functioning in patients with gastroparesis.

Despite improvements in 89% of patients' gastrointestinal symptoms, most patients still had some sort of gastroparesis symptoms (eg, occasional to frequent vomiting or abdominal pains). Although it is clear that gastric neurostimulation from ET does not cure patients of gastroparesis, this study shows that ET has the ability to alleviate patients' symptoms to varying degrees. Past studies including those of Velanovich[4] and McCallum et al[5] have shown similar findings. In some instances, patients reported ET to completely alleviate certain symptoms (vomiting or nausea, usually) while increasing the severity of a different symptom (eg, diarrhea or abdominal pain).

The results of this study do not support the notion proposed by past studies that diabetic patients with gastroparesis respond better to gastric neurostimulation than patients with idiopathic gastroparesis.[12] On the basis of analysis of the GSRS, this study found no significant difference in the responses of patients with diabetic gastroparesis and patients with idiopathic gastroparesis to ET. Given the relatively small sample size of this study, however, further investigation into the response by gastroparesis etiology is needed.

Parkman et al[13] showed the existence of differences in gastroparesis symptoms in patients with and without a history of cholecystectomy. With this in mind, this study also focused on the differences in patient responses to ET with respect to history of cholecystectomy. Interestingly, it was found that symptoms in patients with a history of cholecystectomy responded better to ET than patients without prior cholecystectomy. The improvement in GSRS scores for patients with a history of cholecystectomy was found to be statistically significant, with $P < .01$. This is compared with GSRS improvements in patients without a history of cholecystectomy, which were not statistically significant ($P = .06$).

In some cases, the etiology of gastroparesis has also been linked to anxiety disorders.[14] In this study 44% of gastroparesis patients (n = 11) had some sort of anxiety, depression, or personality disorder. Symptom responses to ET in these patients did not differ significantly from those in patients without anxiety, depression, or a personality disorder.

CONCLUSION

As shown by the vast range and severity of symptoms faced by each patient, gastroparesis is clearly a variable disorder that presents uniquely in each patient. This fact,

which has been well noted in the literature,[15] along with the reality that every patient responds to treatment differently, makes it especially difficult to cure gastroparesis. However, if pharmaceuticals and dietary treatments prove ineffective in relieving gastroparesis symptoms, there is another treatment option—gastric neurostimulation. The results of this study indicate that ET can indeed be used to alleviate gastroparesis symptoms, albeit to varying degrees, in most patients. To improve outcomes with ET, more research is needed detailing the types of patients who respond best to gastric neurostimulation. Improved management of each patient's neurostimulator settings could also be an area of research valuable to improving patient outcomes.

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